EXHIBIT B

Maximum Exposure Guideline

for

Perfluorooctanoic Acid in Drinking Water

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Environmental and Occupational Health Program
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Abstract

Due to the potential presence of perfluorooctanoic acid **(**PFOA) in Maine drinking water, the Maine Center for Disease Control and Prevention (MECDC) developed a health-based Maximum Exposure Guideline (MEG) for PFOA in drinking water. MEGs are typically derived from peer-reviewed reference doses (RfDs) published by authoritative governmental health agencies. To date, there are no PFOA RfDs for lifetime exposures available from any agency the MECDC relies upon to develop chemical specific MEGs. As such, the available State, Federal, and International risk assessments for PFOA were reviewed, along with primary literature, to select a point of departure (POD) and derive a RfD and subsequent MEG. PFOA-induced hepatotoxicity was selected as a sensitive endpoint because it occurs in multiple species, including humans, follows acute, subchronic and chronic exposures, is a relatively sensitive endpoint, and benchmark dose (BMD) modeling results with benchmark dose lower limits (BMDLs) were available. Human oral equivalent doses were derived from individual BMDLs from BMD modeling results in multiple rodent studies that displayed adverse liver effects following oral PFOA exposure. Human equivalent doses were calculated using a pharmacokinetic adjustment factor based on animal-to-human PFOA clearance rates. The geometric mean of the human equivalent doses (0.0018mg/kg/day) was selected as the POD and 3-fold interspecies, 10-fold intraspecies and 10-fold database uncertainty factors were applied to derive a RfD (0.006µg/kg/day). The 10-fold database uncertainty factor was applied to account for potentially more sensitive PFOA-induced health effects identified in animal and human studies. The MEG (0.1µg/L) was calculated from the RfD through application of a standard 70kg adult body weight and 2L/day water intake rate and a 60% data-driven relative source contribution factor.

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1. Overview

This document describes the basis for a Maximum Exposure Guideline (MEG) for perfluorooctanoic acid (PFOA) in drinking water. MEGs are the Maine Center for Disease Control and Prevention's (MECDC) recommendations for concentrations of chemicals in drinking water below which there are minimal risks of adverse health effects from a lifetime of ingestion. MEGs are guidance levels; they are not regulatory standards. MECDC has established procedures for developing MEGs that are largely consistent with U.S. Environmental Protection Agency (USEPA) procedures for deriving drinking water equivalent levels (DWELs) (MECDC, 2011).

It is MECDC standard practice to derive MEGs from reference doses (RfDs) selected from a hierarchy of databases including EPA's IRIS (Integrated Risk Information System), California's Office of Environmental Health Hazard Assessment (CA-OEHHA) Toxicity Criteria, ATSDR's (Agency for Toxic Substances and Disease Registry) Minimal Risk Levels, USEPA Provisional Peer-Reviewed Toxicity Values (PPRTVs), USEPA's Health Effects Assessment Summary Tables (HEAST), and the International Toxicity Estimates for Risk (ITER) database which contains toxicity information from international sources, e.g., Health Canada (MECDC, 2011). As of the finalization of this document there were no RfDs published by any agency listed above for PFOA. As such, a RfD and MEG were derived following review of the current State, Federal, and International PFOA risk assessments and primary toxicity and exposure studies.

2. General PFOA Exposure and Toxicity

2.1 PFOA exposure

PFOA is an anthropogenic perfluorinated compound (PFC) used in numerous industrial processes and consumer products because of its unique heat-, oil- and water-resistant properties. Due to their widespread use, high water solubility, and stable and persistent nature PFCs, including PFOA, are ubiquitous environmental contaminants that adulterate food and drinking water sources worldwide (Lorber et al., 2011 and Post et al., 2012). Consequently, PFOA is commonly detected in human serum. From the most recent National Health and Nutrition Examination Survey (NHANES), the geometric mean and 95th percentile PFOA serum concentration in a representative sample of the U.S. population was 3.07nanograms/milliliter (ng/mL) and 7.50ng/mL, respectively (CDC NHANES, 2013). Furthermore, due to its chemical stability, PFOA is not metabolized and is eliminated slowly in humans with an estimated elimination half-life of 2 to 4 years (Olsen et al., 2007 and Bartell et al., 2010).

2.2 PFOA toxicity, animal studies

In animal models oral exposure to PFOA causes a wide array of non-carcinogenic toxicities (Lau et al., 2007 and Post et al., 2012). PFOA exposure can alter developmental endpoints and disrupt reproductive functions, cause neurological and behavioral abnormalities and modulate the immune system and subsequent immune responses (Lau et al., 2007 and Post et al., 2012). In multiple species hepatic toxicity manifesting as hepatomegaly is commonly observed in response to oral PFOA exposure (USEPA, 2005 and EFSA, 2008). PFOA is a peroxisome proliferator-activated receptor α (PPARα) agonist and both PPARα-dependent and -independent mechanisms underlying adverse developmental, immunomodulatory and hepatic effects have been identified in rodents (Post et al., 2012 and DeWitt et al., 2012). PFOA has also been shown to disrupt endocrine system function in rodents, which may be the cause of observed adverse developmental, reproductive and immune effects (White et al., 2011a).

However, the precise mechanisms underlying these adverse effects are unclear and research is ongoing to better characterize mechanisms of action, sensitive endpoints and dose-response relationships.

Exposure to PFOA has also been shown to induce certain types of tumors in animal models. Chronic exposure studies in rats suggest that PFOA is a potential carcinogen with increased incidences of testicular, pancreatic, liver and mammary tumors observed following chronic PFOA exposures (Sibinski et al., 1983/Butenhoff et al. 2012[1]and Biegel et al., 2001). Based on these animal studies the USEPA in a 2005 draft PFOA human health risk assessment concluded that there is 'suggestive' evidence of carcinogenicity (USEPA, 2005). A subsequent Science Advisory Board (SAB) review in 2006 concluded that according to EPA Cancer Guidelines the available evidence in animals suggests that PFOA is 'likely to be carcinogenic to humans' (USEPA, 2006). However, the USEPA has not developed a cancer slope factor for PFOA and neither the National Toxicology Program (NTP) nor the International Agency for Research on Cancer (IARC) has performed a comprehensive review regarding PFOA carcinogenicity.

2.3 PFOA toxicity, human studies

Epidemiological studies of general, occupationally and contaminated drinking water exposed populations suggest that exposure to PFOA may increase serum cholesterol and uric acid levels, alter thyroid hormone levels and contribute to thyroid disease, and disrupt both male and female hormone levels and reproductive parameters (Table 1). Studies involving a large cohort exposed to PFOA through contaminated drinking water have shown increased incidences of pregnancy-induced hypertension, high cholesterol, thyroid disease and ulcerative colitis within the exposed population (C8 Science Panel, 2012). The human immune system is also sensitive to PFOA, as increased PFOA serum levels in children have recently been associated with decreases in vaccine antibody levels (Grandjean et al., 2012). Additionally, increased concentrations of PFOA in maternal serum from a small cohort of mother-child pairs were associated with decreased humoral immunity and increased incidences of common cold in children under 3 years of age (Granum et al., 2013). Analysis of a cohort of highly exposed adults, demonstrated that individuals with higher PFOA serum levels tended to have lower influenza vaccine antibody titers (Looker et al., 2013). Taken together, there are multiple epidemiological studies that provide evidence that humans are sensitive to PFOA and exposures may cause multiple adverse non-cancer health effects.

In contrast to studies in rats, the carcinogenic potential of PFOA in humans is less clear. Studies involving workers occupationally exposed to PFOA have shown positive trends in kidney, pancreatic and prostate cancers with increasing exposure (Steenland et al., 2010). In a general population of Danish citizens researchers found no positive associations or trends between increasing PFOA serum levels and risk of prostate, bladder, liver or pancreatic cancer (Eriksen et al., 2009). Conversely, researchers evaluating a population exposed to PFOA through a known source of contaminated drinking water observed increased risks of kidney, testicular, prostate and ovarian cancers and non-Hodgkin lymphoma in individuals exposed to greater concentrations of PFOA (Vieira et al., 2013 and Barry et al., 2013).While the evidence is limited, there is concern based on these recent evaluations that long-term exposure to PFOA in drinking water may be risk factor for developing specific cancers (Table 1).

[1] The Sibinski et al., 1983 2-year rat study was originally carried out from 1981-1983. The study results were only available to the U.S. EPA as a public docket report (Administrative record-226). In 2012, the original 1983 study results, often cited as Sibinski L.J. 1987, were published in the journal Toxicology as Butenhoff, J.L., Kennedy, G.L., Chang, S.C., Olsen, G.W. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology. 2012. 298(1-3):1-13.

Table 1. Summary of results from recent epidemiology studies focusing on PFOA and PFCs.

Study and population type	Cohort and sample size	Study focus	Mean PFOA serum level (ng/mL) [a]	PFOA serum range (ng/mL)	Key study findings associated with PFOA
Darrow et al., 2013, Cross-sectional exposed population	C8 studies, n = 1630	Birth outcomes	31.0	0.6 – 459.5	Increased incidence of pregnancy induced hypertension
Steenland et al., 2009, Cross-sectional exposed population	C8 studies, n = 46,294	Cholesterol levels	80.3	0.25 – 17,557	Increased total cholesterol levels in adults
Lopez-Espinosa et al., 2012, Cross-sectional exposed population	C8 Studies, n = 10,725	Thyroid disease	29.3 (median)	13.1 – 67.7 (IQR) [b]	Increased odds ratio for thyroid disease in children age 1-17
Winquist et al., 2014, Cross-sectional exposed population	C8 Studies n = 32,254	Thyroid disease	86.6	0.8 – 3,168	Increased hazard ratio for thyroid disease in adult men
Gallo et al., 2010, Cross-sectional exposed population	C8 studies n = 46,452	Liver function	28.0 (median)	13.5 – 70.8 (IQR)	Positive association between increasing PFOA serum levels and increased serum alanine transaminase
Looker et al., 2013 Cross-sectional exposed population	C8 studies, n = 411	Immune response	33.7 (geometric mean)	0.25 – 2,140	Decreased influenza antibody titers in adults >18 with increasing PFOA serum levels
Steenland et al., 2013 Cross-sectional exposed population	C8 studies, n = 32,254	Autoimmune disease	87	13 – 68 (IQR)	Increased relative risk of ulcerative colitis with increasing cumulative PFOA exposures in adults
Barry et al., 2013, Cross-sectional exposed population	C8 studies, n = 32,254	Cancer	24.2 (median)	0.25 – 22,412	Increased hazard ratio for kidney and testicular cancer with increasing estimated cumulative PFOA serum levels in adults
Vieria et al., 2013 Cross-sectional exposed population	C8 studies, n = 32,254	Cancer	24.2 (median)	0.25 – 22,412	Increased odds ratio for testicular, kidney, prostate, ovarian cancer and non-Hodgkin's lymphoma with increasing modeled PFOA serum levels in adults
Nelson et al., 2010, Cross-sectional general population	NHANES 2003-2004, n = 860	Cholesterol levels	4.6	0.1 – 37.3	Increased association between increasing PFOA serum levels and increased total and non-high density cholesterol
Melzer et al., 2010, Cross-sectional general population	NHANES 1999 – 2005, n = 2,066	Thyroid disease	4.25	0.1 – 123	Increased incidence of thyroid disease in adult women
Geiger et al., 2013 Cross-sectional general population	NHANES 1999 – 2008, n = 1,772	Uric acid levels	4.3	<2.9 – >5.4	Association between increasing PFOA and PFOS serum levels and uric acid levels and hyperuricemia in children age 12-18
Kristensen et al., 2013, Prospective general population	Danish pregnancy cohort, n = 337	Reproductive	3.6 (median)	0.1 – 19.8	Later age of menarche in daughters exposed to higher PFOA levels in utero
Vested et al., 2013, Prospective general population	Danish pregnancy cohort, n = 169	Reproductive	3.8 (median)	1.26 – 16.57	Decreased sperm levels and increased reproductive hormone levels in men born to mothers with higher in utero PFOA serum levels
Halldorsson et al., 2012, Prospective general population	Danish pregnancy cohort, n = 665	Weight gain	3.7 (median)	0.1 – 19.8	Increased weight and BMI in females born to mothers with higher PFOA serum levels
Eriksen et al., 2009 Prospective general population	Danish diet, cancer and health cohort, n = 1240	Cancer	6.8 (median, men) 6.0 (median, women)	3.1 – 14.1 (5%-95% percentile, men) 2.6 – 11.0 (5%-95%, women)	No significant associated risk between PFOA serum levels and prostate, bladder, pancreatic or liver cancer in adults
Grandjean et al., 2012, Cross-sectional general population	Faroe Island cohort, n = 587	Immune response	4.06 (geometric mean)	3.33 – 4.96 (IQR)	Decreased vaccine antibody levels in children age 5-7 with increasing PFOA and PFOS serum levels
Granum et al., 2013 Cross-sectional general population	Norwegian mother child cohort, n = 90	Immune response	1.1	0.2 – 2.7	Decreased vaccine antibody levels and increased incidence of common colds in children at age 3 with increasing PFOA and PFC maternal serum levels

a. Serum levels for PFOA from the most recent NHANES biomonitoring data for the general U.S. population are geometric mean of 3.07ng/mL (2.81-3.36, 95% confidence interval) and 95th percentile of 7.50ng/mL (6.20-9.70, 95% confidence interval) (CDC NNHAES, 2013).

b. IQR is interquartile range.

3. State, Federal and International Risk Assessments for PFOA

Currently there are no Federal drinking water standards or regulations for PFOA and few states have developed individual guidelines or regulations. New Jersey, Minnesota and North Carolina are the only States that have developed drinking water guidance levels for PFOA (Table 2). In 2005 the USEPA summarized and reviewed the most recent PFOA toxicity data, but did not complete a full risk assessment (USEPA, 2005). In 2009 the USEPA Office of Water developed a Provisional Health Advisory (PHA) for short-term PFOA exposures, but as of completion of the MECDC PFOA MEG the USEPA has not developed a final oral RfD for lifetime exposures nor a maximum contaminant level (MCL) for PFOA in drinking water.

3.1 New Jersey, 2007

New Jersey established a health-based guideline of 0.04micrograms/liter (µg/L) PFOA in drinking water (New Jersey, 2007). This value is based on a chronic dietary exposure study in which male and female rats were exposed to PFOA as ammonium perfluorooctanoate (APFO) at 0, 30 and 300 parts per million (ppm) in their diet (Sibinski et al., 1983/Butenhoff et al. 2012). Reduced body weight in females was selected as the critical endpoint. A no observed adverse effect level (NOAEL) for the critical endpoint was identified at 30ppm. Based on the mean dietary intake for female rats the dose at 30ppm was estimated at 1.6milligrams/kilogram per day (mg/kg/day) (USEPA, 2005). The 1.6mg/kg/day NOAEL was used to estimate an internal serum concentration in female rats of 1800µg/L. This serum level is based on an area under the curve (AUC) estimate (44µg-hour/mL) for PFOA clearance from a one-compartment pharmacokinetic (PK) model developed by the USEPA using measured serum and clearance data from a separate oral gavage study in rats (USEPA, 2005). A total uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies sensitivity) was applied to the 1800µg/L serum level in female rats to estimate a target human serum level of 18µg/L. A relative source contribution (RSC) factor of 0.2 was used to calculate the target contribution to human serum from drinking water of 4µg/L. New Jersey then used a 100:1 ratio between PFOA serum concentrations and drinking water to derive the drinking water guidance value for PFOA from the target human serum level. The 100:1 ratio is based on a several studies where PFOA serum levels from populations drinking PFOA contaminated water were approximately 100-fold greater than PFOA concentrations in the water (Emmett et al., 2006 and Post et al., 2012). The 100:1 ratio was applied to the 4µg/L target human serum concentration to derive the health-based drinking water concentration of 0.04µg/L.

3.2 European Food Safety Authority, 2008

In 2008 the European Food and Safety Authority (EFSA) reviewed and evaluated the available PFOA toxicity studies and derived a tolerable daily intake (TDI) for PFOA (EFSA, 2008). TDIs are expressed on a per body weight basis and represent levels of a substance that can be ingested over a life-time without appreciable health risk (EFSA, 2008). The PFOA TDI was derived following a hazard identification process and selection of several multiple-dose subchronic, chronic and developmental and reproductive PFOA toxicity studies in animals to identify the most sensitive endpoint (EFSA, 2008). Hepatocellular hypertrophy and increased liver weight was identified as the most sensitive endpoint based on the lowest NOAEL from a 13 week oral exposure study in male rats (EFSA, 2008). The EFSA then reviewed benchmark dose modeling (BMD) studies performed by the Committee on Toxicity (COT) that evaluated and identified individual BMDs for a 10% change in adverse liver effects from four separate animal studies (EFSA, 2008).The COT's evaluation included BMD modeling results from both short-term in utero and chronic 2-year exposure studies in either female mice or male rats (Table 3) (EFSA, 2008). The lower bound of the 95% confidence limit on the BMD (BMDL) values ranged from

0.3 – 0.7mg/kg/day. The lowest BMDL of 0.3mg/kg/day was selected as the point of departure (POD). A total uncertainty factor of 200, a 100-fold factor for combined interspecies and intraspecies uncertainty and a 2-fold factor to account for pharmacokinetic uncertainties, was applied to the POD to derive the TDI of 1.5µg/kg/day. This TDI corresponds to a 52.5µg/L drinking water equivalent level for a 70kg adult drinking 2L of water/day and a 10.5µg/L drinking water standard from application of a 20% relative source contribution.

3.3 Minnesota, 2008

The Minnesota Department of Health (MDH) developed a groundwater Health Risk Limit (HRL) of 0.3µg/L for PFOA (MDH, 2008). The HRL is based on a 6-month exposure study in which male cynomolgus monkeys received oral capsule doses of 0, 3, 10 and 30/20[2] mg/kg/day PFOA as APFO (Butenhoff et al., 2002). BMD modeling using serum concentrations and increased liver weight as the sensitive endpoint were used to derive a POD. The BMD modeling fit internal PFOA serum concentrations as the dose measure and liver-to-brain weight ratio as the critical endpoint to a linear model (Butenhoff et al., 2004). The benchmark response (BMR) was a 10% change in the liver-to-brain ratio (Butenhoff et al., 2004). The resulting BMDL, from the 95% lower confidence limit, of 23µg/mL PFOA serum concentration was selected as the POD. The BMD was not reported (Butenhoff et al., 2004). An oral human equivalent dose of 2.3µg/kg/day was derived by multiplying the 23µg/mL serum-based POD by PFOA clearance in humans. PFOA clearance was calculated based on first order kinetics with a human half-life of 1387 days and a volume of distribution of 0.198L/kg rounded to 0.2L/kg (human PFOA clearance = (0.2L/kg)(ln(2)/1387days) = 0.0001L/kg/day). A total uncertainty factor of 30 (3 for interspecies extrapolation and 10 for intraspecies sensitivity) was applied to the oral human equivalent dose to derive a reference dose (RfD) of 0.077µg/kg/day. Using the RfD, a RSC factor of 0.2, and a water intake rate of 0.053L/kg/day (corresponding to 3.7L/day for a 70kg individual) the calculated chronic non-cancer HRL was 0.3µg/L.

3.4 U.S. EPA, 2009

The USEPA Office of Water developed a PHA of 0.4µg/L for short-term (10-day) PFOA exposure through drinking water using a child exposure scenario (USEPA, 2009). The PHA is based on a developmental study in which pregnant mice were exposed via oral gavage to 0, 1, 3, 5, 10, 20 or 40mg/kg PFOA from gestational day 1 through 17 (Lau et al., 2006). Increased maternal liver weight at term was selected as the critical endpoint. Benchmark dose modeling was performed using external administered doses as the dose measure and a BMR of 10% for the increase in maternal liver weight at term (USEPA, 2009 and EFSA, 2008). While the BMD modeling methods were not described, the BMD and BMDL were reported as 0.52 and 0.46mg/kg/day, respectively (USEPA, 2009 and EFSA, 2008). The BMDL of 0.46mg/kg/day was selected as the POD. A toxicokinetic extrapolation factor of 81 was calculated based on the ratio of PFOA clearance in female mice to clearance in humans. PFOA clearance in female mice was calculated using a half-life of 17 days and a volume of distribution of 0.198L/kg (mouse PFOA clearance = (0.198L/kg)(ln(2)/17days) = 0.0081L/kg/day) and in humans with a half-life of 1387 days and a volume of distribution of 0.198L/kg (human PFOA clearance = (0.198L/kg)(ln(2)/1387days) = 0.0001L/kg/day). Application of the toxicokinetic factor, a 3-fold factor for interspecies toxicodynamics, 10-fold factor for intraspecies sensitivity, a 10kg child body weight, a water consumption rate of 1L/day and a 0.2 RSC factor to the 0.46mg/kg/day POD yielded the PHA of 0.4µg/L.

[2] Dosing in the highest dose group began with 30mg/kg/day, but due to overt toxicity the dose was reduced to 20mg/kg/day following a two week recovery period (Butenhoff et al., 2002).

3.5 North Carolina, 2012

North Carolina's Secretary's Science Advisory Board on Toxic Air Pollutants (NCSAB) developed an Interim Maximum Allowable Concentration (IMAC) of 1µg/L PFOA in groundwater (NCSAB, 2012). The NCSAB IMAC is based on the 2002 Butenhoff male cynomolgus monkey study, where monkeys were administered oral doses of 0, 3, 10 and 30/20[2] mg/kg/day PFOA as APFO for 6 months (Butenhoff et al., 2002). Increased liver weight, expressed as the ratio of liver-to-brain weight, was selected as the most sensitive endpoint. BMD modeling was performed to derive POD. A linear model was fit to the chosen endpoint using PFOA serum concentrations as the dose measure. The BMR was a 10% increase in the liver-to-brain weight ratio. A BMD of 40µg/mL was derived from this dose-response modeling. The NCSAB did not report the BMDL for this endpoint. The 40µg/mL BMD was selected as the lowest POD and used to estimate an external dose in humans of 336µg/person/day for a 70kg individual, by applying a serum-to-external exposure level conversion factor of 0.12µg ingested/kg/µg/mL (NCSAB, 2012). The 0.12 conversion factor was derived from a physiological-based pharmacokinetic (PBPK) model used to scale PFOA serum levels in monkeys to humans (NCSAB, 2012). A total uncertainty factor of 30 (3 for interspecies extrapolation and 10 for intraspecies sensitivity), a RSC factor of 0.2, and a 2L/day water consumption rate were applied to the 336µg/person/day exposure level, to yield an IMAC of 1µg/L.

Table 2. Comparison of State and Federal PFOA drinking water guidelines.

Agency	Key study, species and sex	Primary Endpoint	Approach	BMR	POD	PK model	Human eq. dose [a]	Water Intake	Body weight	RSC	Uncertainty factors	Drinking water level
New Jersey DEP, 2007	Sibinski et al., 1983, rat, female	Decreased body weight	NOAEL, dietary intake dose	n.a.	NOAEL, 1.6mg/kg/day	AUC	n.a.	n.a. [b]	n.a. [b]	20%	10 interspecies 10 intraspecies	**0.04 µg/L**
Minnesota MDH, 2008	Butenhoff et al., 2002, monkey, male	Liver-to-brain weight ratio	BMD modeling, internal serum concentration	10% change	BMDL, 23µg/mL	One-compartment	2.3µg/kg/day	3.7L/day [c]	70kg [c]	20%	3 interspecies 10 intraspecies	**0.3 µg/L**
USEPA OW, 2009 (Short-term advisory)	Lau et al., 2006, mouse, female	Increased maternal liver weight	BMD modeling, administered dose	10% change	BMDL, 0.46mg/kg/day	One-compartment	5.7µg/kg/day	1L/day	10kg	20%	3 interspecies 10 intraspecies	**0.4 µg/L**
North Carolina SAB, 2012	Butenhoff et al., 2002, monkey, male	Liver-to-brain weight ratio	BMD modeling, internal serum concentration	10% change	BMD, 40µg/mL	PBPK	4.8µg/kg/day	2L/day	70kg	20%	3 interspecies 10 intraspecies	**1 µg/L**
Maine CDC, 2014	Multiple studies, mouse/rat, female/male	Increased liver weight/ hepatocyte enlargement	BMD modeling, administered dose	10% change	BMDL, 0.42mg/kg/day [d]	One-compartment	1.8µg/kg/day [d]	2L/day	70kg	60%	3 interspecies 10 intraspecies 10 database uncertainty	**0.1 µg/L**

a. Human equivalent (eq.) doses were estimated for comparison purposes using methods described in individual risk assessments. New Jersey used serum levels estimated in female rats to extrapolate a human serum level rather than an oral human equivalent dose.
b. New Jersey did not use a standard water intake or body weight, but rather a 1:100 drinking water concentration-to-serum concentration ratio was used to calculate the level of PFOA in drinking water from an estimated serum level in humans.
c. Minnesota used a time-weighted average intake rate for the first 19 years of life of 0.053L/kg/day. The water intake rate of 3.7L/day and adult body weight of 70kg are displayed in the table for comparison purposes only.
d. The BMDL is the geometric mean of the BMDLs identified by the EFSA (Table 3). The geometric mean of the human equivalent doses, 1.8µg/kg/day, was calculated individually from study-specific BMDLs and PK-adjustment factors and was used to derive a RfD and the MECDC MEG.

4. PFOA Maximum Exposure Guideline Derivation

To date, no oral RfD or cancer slope factor/cancer classification for PFOA are available in the toxicity databases the MECDC uses to select RfDs and derive MEGs. Therefore, the MECDC reviewed the available Federal, State and International PFOA risk assessments and primary literature to develop a RfD and MEG for PFOA in drinking water. Following standard risk assessment methodology, largely in line with USEPA risk assessment guidelines for drinking water equivalent levels, the MECDC selected a sensitive endpoint and derived a POD based on BMD modeling results from multiple studies. A RfD was derived from the POD following application of several uncertainty factors and the PFOA MEG calculated using the RfD, a standard adult body weight and water intake rate and a RSC factor derived from human serum and exposure data.

4.1 Selection of a sensitive endpoint and POD

The MECDC began with review of the current State, Federal and International risk assessments for PFOA and recent animal and human epidemiology studies involving PFOA exposure. Following review of the health-based risk assessments and primary literature the MECDC selected adverse liver effects as the sensitive endpoint to derive a POD. Adverse liver effects were selected because they have been shown to occur in multiple species, including humans, are dose dependent, are a relatively sensitive endpoint and occur following acute, subchronic and chronic exposures. This is in line with the USEPA PHA, Minnesota HRL, North Carolina IMAC and EFSA TDI risk assessments, which are all based on adverse liver effects in animal models. The New Jersey health-based drinking water guidance level for PFOA is based on decreased body weight and altered hematological parameters, although health-based values from liver endpoints were derived, the body weight endpoint yielded the most health protective value (New Jersey, 2007). While adverse liver effects were used to derive a POD, review of the primary literature brought forth concerns that hepatotoxicity may not be the most sensitive PFOA-induced endpoint in animals and concerns regarding the relevance of emerging epidemiological studies in deriving a POD. Nonetheless, at this time adverse liver effects were seen as having the strongest weight-of-evidence to support derivation of a RfD. Concerns over more sensitive endpoints and human studies were addressed with uncertainty factors.

Recent studies in mice suggest the development of mammary gland tissue in female offspring is highly sensitive to gestational PFOA exposure (Macon et al., 2011 and White et al., 2011b). Pups from dams orally exposed to PFOA, either for the full gestational term or from gestational days 10-17, displayed significantly inhibited mammary gland development (Macon et al., 2011). Offspring from the full gestational exposure model also displayed significant increases in liver weight with no observed NOAEL. In the late gestational model increased liver weight was observed only in the highest dose group, whereas altered mammary gland growth was observed in all dose groups with no NOAEL identified (Macon et al., 2011). This study suggests that although hepatomegaly is a sensitive endpoint, developmental mammary gland effects may occur at lower doses. Consequently, adverse mammary gland development may be a considerably more sensitive endpoint. Accordingly, Post and colleagues used measured serum level and mammary gland development data from the late gestational exposure model in mice to derived BMDs and BMDLs that were approximately 1000-fold lower than the BMD and BMDL derived from serum levels and increased liver-to-brain weight ratios in cynmologus monkeys (Post et al., 2012 and Butenhoff et al., 2004). While developmental effects of the mammary gland are noteworthy, these effects have only been tested in mice and the mouse strain used in these experiments may be particularly sensitive, as other strains have been shown to be less sensitive to this PFOA-induced effect (Macon et al., 2011 and Yang et al., 2009). Overall, because PFOA-induced mammary gland effects have only been tested in mice, with a potential difference in strain sensitivity,

and in comparison with liver toxicity there are a limited number of studies regarding mammary gland development following PFOA exposure, the adverse mammary gland development endpoint was not used to derive a POD.

Review of the primary literature also highlighted the potential importance of emerging epidemiological studies showing associations between PFOA exposure and adverse reproductive, cardiovascular, thyroidal, and immunological health effects, among others, in humans (Table 1). While there is mounting evidence for adverse health effects in humans following PFOA exposure, no single endpoint from an epidemiology study was considered suitable for quantitative risk assessment. To better assess human health effects from PFOA exposure through drinking water, PFOA serum level data from select epidemiology studies were used to estimate PFOA drinking water concentrations using a 100:1 serum-to-drinking water concentration ratio (Table 4). The lowest estimated PFOA drinking water levels that were associated with adverse human health effects came from studies that evaluated immune effects in children (Table 4). BMD modeling results from the Faroe Island childhood vaccine study suggest that decreased vaccine antibody levels are a highly sensitive PFC-induced health effect as the BMDL is approximately 800-fold lower than the serum-derived BMDL from increased liver weight in non-human primates (Grandjean et al., 2013 and Butenhoff et al., 2004). It would be possible to derive a RfD based on these human BMD modeling results. However, the primary concern with these human immunological studies, as well as other epidemiological studies involving PFOA, is presence of additional PFCs, including perfluorooctane sulfonic acid (PFOS), and possibly other contaminants. Due to structural similarities, individual PFCs are likely to have similar toxicities, which can confound results from studies trying to attribute adverse health effects to a single PFC. Both PFOA and PFOS are associated with decreasing antibody levels in children and it is difficult to say with certainty that an individual PFC is the causative agent (Grandjean et al., 2013 and Granum et al., 2013). Due to the inability to single out the immunosuppressive effects of PFOA from PFOS and other PFCs, the BMD modeling results from the children's vaccine study were not used to derive a POD. Instead, concerns over this PFOA/PFC-induced health effect and additional human health effects were taken into account with uncertainty factors. Overall, due to the lack of a single human epidemiological study sufficient for quantitative risk assessment, the process of selecting a sensitive endpoint and POD focused on adverse liver effects in animal studies.

Hepatotoxicity following PFOA exposure is observed in multiple species including mice, rats and monkeys (USEPA, 2005, EFSA, 2008 and Gallo et al., 2012). The hepatotoxic effects include increased liver enzyme levels, increased liver weight, hepatocyte enlargement and proliferation and malignant cell growth (USEPA, 2005 and EFSA, 2008). PFOA-induced liver toxicity, measured as absolute or relative liver weight, is often a highly sensitive endpoint following both subchronic and chronic exposure (USEPA, 2005 and EFSA, 2008). For example, the USEPA PHA is based on increased liver weight in female mice from a developmental study in which maternal liver weight was the most sensitive endpoint as compared to developmental endpoints that occurred at higher doses (Lau et al., 2006 and USEPA, 2009). Increased maternal liver weight occurred after 17 days of exposure to 1, 3, 5, 10, 20 or 40mg/kg/day PFOA and was dose-dependent (Lau et al., 2006). In a 13 week subchronic dietary exposure study, male rats exposed to 0, 0.06, 0.64 1.94 and 6.5mg/kg/day PFOA displayed significant increases in relative liver weight at doses greater than 0.06mg/kg/day (Perkins et al., 2004 and USEPA, 2005). Increased liver weight in this study also occurred following 4 and 7 week exposures (Perkins et al., 2004 and USEPA, 2005). In chronic 2-year studies, primarily evaluating PFOA carcinogenicity, increased hepatocyte enlargement and liver weight were observed along with increased rates of liver adenomas in male rats (Sibinski et al., 1983/Butenhoff et al. 2012 and Biegel et al., 2001). Although increased liver weight in response to xenobiotics is often ascribed as an adaptive and reversible effect, chronic studies in male rats indicate that long-term PFOA exposure results in irreversible liver damage.

The primary mechanism of action underlying PFOA-induced hepatotoxicity in rodents is thought to be mediated by PPARα activation (USEPA, 2005). It is uncertain whether this mechanism is entirely relevant to humans, as they typically express less hepatic PPARα as compared to rodents (Andersen, 2008). However, non-human primates, which have similar PPARα expression as humans, displayed increases in relative liver weight following six-month oral PFOA exposure, indicating that PFOA-induced hepatotoxicity is not limited to sensitive rodent species (Butenhoff et al., 2002). Adverse liver effects are also likely to be directly relevant to humans, as increasing serum levels of alanine aminotransferase (ALT), a marker of hepatocellular damage, was recently associated with increasing PFOA serum levels in a population exposed to PFOA through contaminated drinking water (Gallo et al., 2012). Despite potential divergent mechanisms of action, mice, rats, non-human primates and humans all display some form of hepatotoxicity in response to PFOA.

Rather than select a single study to derive a POD based on adverse liver effects, several studies were used because of similar responses in the liver to varying administered PFOA doses. BMD modeling from studies in male rats and female mice resulted in closely spaced benchmark doses for a 10% change in liver weight or hepatocyte enlargement in response to oral PFOA exposure (Table 3) (EFSA, 2008). The EFSA/COT performed BMD modeling with data from several studies that included both subchronic and chronic dosing regimens with adverse liver effects in both female mice and male rats (EFSA, 2008). The BMDs from these studies are similar across species and time frames, ranging from 0.52 – 1.1mg/kg/day (Table 3) (EFSA, 2008). While these BMD modeling results are from studies in rodents, for comparison the BMD for a 10% increase in absolute liver weight in cynomolgus monkeys following oral PFOA exposure for 26 weeks is 0.35mg/kg/day[3] (Table 3). The BMDs from separate studies in three different species for adverse liver effects in response to PFOA are reasonably similar (Table 3). Thus, rather than select one BMD and subsequent BMDL from a single study in an individual species as a POD, human equivalent doses were derived from the individual BMDLs described by the EFSA and the geometric mean of the human equivalent doses was selected as the POD (Table 3) (EFSA, 2008).

Due to large differences in the half-life of PFOA between species, human equivalent doses were calculated separately by dividing the individual BMDLs by a species-specific pharmacokinetic (PK) adjustment factor. The PK-adjustment factor is a ratio of PFOA clearance between animals and humans based on a one-compartment model with a similar volume of distribution (0.2L/kg) between species, where clearance = (volume of distribution)(ln(2)/species-specific half-life) (USEPA, 2009). The half-life in mice is 19 days in males and 17 days in females, whereas in rats the half-life is 4-6 days in males and only 2-4 hours in females (Lau et at., 2007, USEPA, 2009 and Post et al., 2012). In monkeys the half-life of PFOA is 30 days in females and 21 days in males (Lau et al., 2007 and Post et al., 2012). In humans, two separate studies estimated a half-life of 2.3 and 3.8 years, with no apparent difference between males and females (Olsen et al., 2007 and Bartell et al., 2010). To calculate clearance for female mice, male rats and male monkeys the half-life values of 17 days, 5 days and 21days, respectively, were utilized. For humans the half-life of 3.8 years (1387 days) was used to calculate PFOA clearance (USEPA, 2009)[4]. The resulting PK factors of 82 for female mice, 277 for male rats and

[3] The BMD of 0.35mg/kg/day for increased absolute liver weight in male cynomolgus monkeys was derived using EPA Benchmark Dose software (BMDS version 2.3.1) and data from Butenhoff et al., 2002. Administered dose was used as the dose measure with the highest dose group dropped from analysis. The BMD was defined as a 10% benchmark dose response in increased absolute liver weight from an exponential model that fitted the data appropriately based on goodness-of-fit parameters (USEPA, 2012). Due to considerable variance in absolute liver weight in the control and two dose groups, the BMDL, 95% lower bound of the BMD, was considered statistically unstable for use as a BMDL to derive a human equivalent dose.

[4] The human half-life of 3.8 years was selected over the 2.3 year estimate due to the fact that the 3.8 year PFOA half-life is derived from multiple PFOA serum measurements up to 5 years post-exposure (Olsen et al., 2007). Whereas the 2.3 year half-life estimate is derived from only 7 to 12 month post-exposure serum measurements (Bartell et al., 2010).

66 for male monkeys were then applied to the BMDLs identified by the EFSA to calculate human equivalent doses, which ranged from 0.0010 – 0.0056mg/kg/day (Table 3). The geometric mean of the six human equivalent doses, 0.0018mg/kg/day, was selected as the POD.

External oral administered doses were used to derive a POD rather than measured internal serum doses. In most cases, the use of internal doses is preferable over external administered dose for deriving a RfD (USEPA, 2011). Internal dose can directly account for species-specific pharmacokinetics and reduce interspecies uncertainty (USEPA, 2011). Regarding PFOA, use of an internal serum dose is beneficial because PFOA is not metabolized and the volume of distribution is similar between species, making it easier to compare adverse effects across species, including humans (Butenhoff et al., 2004 and USEPA, 2009). However, when evaluating BMD modeling results with internal serum levels as the dose metric there was considerable inter-animal serum level variability, particularly in the cynomolgus monkey study (Butenhoff et al., 2004). Standard BMD modeling takes into account the variability within the response, but does not account for any variability in the dose measure. Variability in the dose measure can undermine the usefulness and relevance of standard BMD modeling methods. Additionally, not all animal studies measured internal PFOA serum concentrations. To compare dose-response results based on internal dose measure would require pharmacokinetic estimations from external doses for some studies, which could potentially introduce undue uncertainty. For these reasons external oral doses were relied upon to derive a POD rather than internal measured serum concentrations.

Table 3. Liver endpoint BMD modeling summary (table modified and expanded from EFSA, 2008).

Study (Route of exposure)	Effect	Species (Strain/Stock)	Sex	Exposure Duration (Weeks)	BMD (mg/kg/day)	BMDL (mg/kg/day)	PK-Adjustment Factor [a]	Human Equivalent Dose (mg/kg/day) [b]
Lau et al., 2006 (oral gavage)	Increased absolute maternal liver weight	Mouse (CD-1)	Female	GD 1-17 [c]	0.52	0.46	82	0.0056
Perkins et al., 2004 [d] (oral dietary)	Increased absolute liver weight	Rats (Crl:CD BR)	Male	4	0.6	0.4	277	0.0014
Perkins et al., 2004 (oral dietary)	Increased absolute liver weight	Rats (Crl:CD BR)	Male	7	0.69	0.29	277	0.0010
Perkins et al., 2004 (oral dietary)	Increased absolute liver weight	Rats (Crl:CD BR)	Male	13	0.89	0.44	277	0.0016
Sibinski et al., 1983 (oral dietary)	Hepatocyte enlargement	Rats (Crl:CD BR)	Male	104	1.1	0.74	277	0.0027
Butenhoff et al., 2004 (oral gavage)	Increased absolute liver weight	Rats (Crl:CD BR)	Male	GD 15-17 [c]	0.78	0.31	277	0.0011
Butenhoff et al., 2002 [e] (oral capsle)	Increased absolute liver weight	Monkeys (cynomolgus)	Male	26	0.35	n.a. [e]	66	0.0053[e]

a. The PK-adjustment factor is the ratio of PFOA clearance (CL) between animals and humans and is based on a one-compartment model at steady-state with similar volume of distribution for PFOA between species (0.2L/kg) and species-specific half-life (USEPA, 2009).
CL_{humans} = (0.2L/kg)(ln(2)/1387days) = 0.0001L/kg/day
$CL_{male\ rats}$ = (0.2L/kg)(ln(2)/5days) = 0.0277L/kg/day, PK-adjustment factor = (0.0277L/kg/day/0.0001L/kg/day) = 277
$CL_{female\ mice}$ = (0.2L/kg)(ln(2)/17days) = 0.0082L/kg/day, PK-adjustment factor = (0.0082L/kg/day/0.0001L/kg/day) = 82
$CL_{male\ monkey}$ = (0.2L/kg)(ln(2)/21days) = 0.0066L/kg/day, PK-adjustment factor = (0.0066L/kg/day/0.0001L/kg/day) = 66
b. Human equivalent dose = BMDL/PK-Adjustment Factor.
c. GD is gestational day where the exposure duration is in days.
d. The Perkins et al., 2004 was a single study that evaluated toxicity at three different time points, 4, 7 and 13 weeks (Perkins et al., 2004).
e. The Butenhoff et al., 2002 monkey study is listed for comparison purposes only. The BMD for absolute liver weight was derived by the MECDC. The resulting BMDL was considered statistically unstable due to considerable inter-animal variability in the control group liver weight measure (mean liver weight 60.2g, 95% confidence interval 16.3, 104.1). The human equivalent dose was calculated using the BMD and shown for comparison purposes only.

4.2 Uncertainty factors

To derive a RfD for PFOA several uncertainty factors were applied to the POD. Differences in the pharmacokinetics of PFOA between animals and humans is largely addressed with the PK-adjustment factors used to calculate the human equivalent doses from female mice and male rats (Table 3). However, there is still uncertainty regarding differences in the mechanism of action and overall toxicodynamics of PFOA between animals and humans such that a 3-fold interspecies uncertainty factor was warranted. Application of a 3-fold interspecies uncertainty factor is also consistent with other State and Federal human health risk assessments for PFOA (Table 2). A 10-fold intraspecies uncertainty factor was applied to account for sensitive human individuals/populations. Application of a 10-fold intraspecies uncertainty factor follows standard risk assessment guidelines when RfDs are derived from animal studies and no other attempts have been made to address sensitive human populations (USEPA, 2000). A subchroninc-to-chronic uncertainty factor greater than 1 was considered unnecessary because the POD based on adverse liver effects was derived from acute, subchronic and chronic studies. The BMDLs from both short and long term studies were all in close agreement, ranging from only 0.29mg/kg/day to 0.74mg/kg/day (Table 3). Additionally, the PK-adjustment factors used to calculate the human equivalent doses partially takes into account chronicity due to the longer estimated half-life in humans as compared to female mice and male rats. Lastly, a 10-fold database uncertainty factor was applied to account for recently identified and potentially more sensitive endpoints in both animals and humans. For the purposes of risk assessment, the toxicological database for PFOA is considered complete according to USEPA guidelines[5] (USEPA, 2000). However, a database uncertainty factor was used to address these additional concerns rather than a modifying factor. A database uncertainty factor was used partly due to the infrequent use of modifying factors in recent risk assessment methodology and a review of USEPA risk assessment guidelines in 2002 suggests that uncertainties addressed by modifying factors should simply be addressed within the database uncertainty factor with proper justification (USEPA, 2002).

Although PFOA-induced hepatotoxicity is observed in multiple species, including humans, there is some uncertainty that it is the most sensitive endpoint in response to PFOA exposure. Studies in mice have identified the developing mammary gland to be highly sensitive to in utero PFOA exposure (Macon et al., 2012 and White et al., 2011b). BMD modeling studies with serum levels and delayed mammary gland development suggest that the mammary gland development endpoint in sensitive mice is approximately 1000-fold lower than the liver endpoint in non-human primates (Post et al., 2012 and Butenhoff et al., 2004). Results from human and animal studies also suggest that the immune system is highly sensitive to PFOA and PFC exposures. Epidemiology studies involving children from the Faroe Islands demonstrated that children with increasing PFOA and PFOS serum levels displayed decreased tetanus and diphtheria antibody levels (Grandjean et al., 2012). From BMD modeling studies, decreasing antibody levels in these children were shown to occur at approximately 800-fold lower serum levels than the BMD based on serum levels from increased liver weight in non-human primates (Grandjean et al., 2013). In a Norway mother-infant population, children under 3 years of age born to mothers with higher PFOA/PFC serum levels displayed decreased rubella vaccine antibody titers and increased incidences of the common cold (Granum et al., 2013). In concordance with these human immunological studies, immune studies in animals have demonstrated that exposure to PFOA is largely immunosuppressive

[5] The database for PFOA toxicity is considered complete according to USEPA guidelines in that there are:
- Two adequate mammalian chronic toxicity studies, by the appropriate route in different species, one of which must be a rodent.
- One adequate mammalian multi-generation reproductive toxicity study by an appropriate route.
- Two adequate mammalian developmental toxicity studies by an appropriate route in different species.

(DeWitt et al., 2009 and DeWitt et al., 2012). In addition, there are a number of recent epidemiological studies from a cohort of highly exposed communities in West Virginia and Ohio that have associated various human health effects with wide ranging PFOA serum levels (Table 1) (C8 Science Panel, 2012). In consequence, the MECDC considers it appropriate to include a 10-fold database uncertainty factor over concerns that in animals the liver endpoint may not be the most sensitive endpoint and that recent epidemiological studies have identified potentially highly sensitive endpoints in humans.

The carcinogenic potential of PFOA is still largely uncertain. Only two chronic exposure studies in rats are available to assess PFOA carcinogenicity. These studies suggest that PFOA induces a tumor triad of liver, testis and pancreatic tumors in male rats and possibly mammary tumors in female rats (Sibinski, 1983/Butenhoff et al. 2012, Biegel et al., 2001 and USEPA, 2005). Based on these studies a science advisory board reviewing PFOA tumorigenicity concluded that there is 'suggestive' evidence that PFOA is carcinogenic with the majority of the board agreeing that PFOA would be classified as "likely to be carcinogenic to humans" (USEPA, 2006). Since the SAB review in 2006, studies involving cancer rates in humans have associated increased serum levels of PFOA to increased rates of testicular, kidney, prostate and ovarian cancers and non-hodgkin lymphomas (C8 Science Panel, 2012, Vieira et al., 2013 and Barry et al., 2013). However, a formal cancer slope factor has not been derived from the PFOA exposure studies in rats. In the absence of a cancer slope factor, it was previously USEPA guidance to include an additional uncertainty factor of 1 – 10 if a chemical is a possible human carcinogen when deriving a RfD for developing drinking water exposure limits (USEPA, 1990). Other States have evaluated drinking water levels associated with PFOA and carcinogenic endpoints in rats and concluded that non-cancer effects occurred at lower doses and PFOA drinking water levels derived from non-cancer endpoints should be protective of cancer in humans[6] (New Jersey, 2007 and NCSAB, 2012). Using the MECDC incremental lifetime cancer risk level of $1x10^{-5}$ for carcinogenic compounds and the serum-based PODs identified from the two cancer studies in rats identified by New Jersey and the NCSAB, the resulting cancer-based PFOA drinking water level would range from 0.2 – 0.6µg/L[6]. Based on these estimated cancer-based PFOA drinking water exposure levels, MECDC does not believe there is a need for an additional uncertainty factor for potential carcinogenicity beyond the 10-fold database uncertainty factor for potentially more sensitive endpoints.

4.3 Relative source contribution

Chemical exposures can occur through various mediums including food, soil, air, water, and consumer products. RSC factors are used to apportion exposure sources such that exposure from a single source does not equal or exceed the RfD (USEPA, 2000). For example, a default 0.2 RSC factor is commonly used to derive drinking water standards from RfDs, which allows only 20% of the total RfD to come from water (USEPA, 2000). A default RSC of 20% is used when there is minimal background contaminant level data in the general population or lack of information regarding characterization of individual exposure sources (USEPA, 2000). When sufficient human background level data or detailed exposure source information are available, then it is often possible to derive a chemical-specific RSC

[6] New Jersey calculated a drinking water level of 0.06µg/L from a dietary exposure study where male rats fed 300ppm PFOA displayed an ~10% increase in Leydig cell, liver, and pancreatic acinar cell adenomas/carcinomas as compared to non-exposed controls (Biegel et al., 2001). A serum level of 572,000µg/L was calculated from the only PFOA dose group, 300ppm (13.6mg/kg/day), and was used to estimate a target human blood level of 5.7µg/L through linear extrapolation from 10^{-1} cancer risk in rats to 10^{-6} risk in humans (New Jersey, 2007). The resulting 0.06µg/L drinking water level, after application of a 100-to-1 serum-to-drinking water ratio, was greater than the lowest drinking water level of 0.04µg/L derived from a non-cancer endpoint (New Jersey, 2007). North Carolina compared a serum-derived BMDL of 203µg/mL (203,000µg/L), resultant from a BMD for a 10% increase in testicular adenomas from a 2-year carcinogenic study in rats, to serum-derived BMDLs of 48 and 62µg/mL from non-cancer endpoints (NCSAB, 2012 and Sibinski et al., 1983/Butenhoff et al., 2012).

factor (USEPA, 2000). In the case of PFOA, there is sufficient background exposure level data from NHANES biomonitoring studies to derive a PFOA-specific RSC for drinking water. NHANES biomonitoring studies, regardless of the route of exposure, indicate that the general U.S. population has a background PFOA serum level of 3.07ng/mL (geometric mean), with the upper 95th percentile having a serum level of 7.5ng/mL (CDC NHANES, 2013). Background serum levels in the general U.S. population are likely due to multiple exposure sources including, but not limited to, food, water, indoor air and dust, and consumer products containing PFOA or PFOA precursors (Lorber et al., 2011). Accordingly, the 95th percentile serum level of 7.5ng/mL from NHANES can be considered as the uppermost background level from all exposure sources for a general population. The background PFOA serum level can then be used to derive a RSC factor through comparison to an estimated PFOA serum level associated with exposure solely from drinking water.

In order to calculate a RSC from the NHANES biomonitoring data the PFOA RfD first needs to be converted to a drinking water equivalent level, i.e. a drinking water concentration for PFOA assuming 100% of the exposure comes from water. To compare the PFOA DWEL to the NHANES background serum level, the DWEL needs to be converted to a corresponding serum level. PFOA serum levels from water concentrations can be estimated through the use of a 100:1 serum-to-drinking water ratio (Emmett et al., 2006). The 100:1 serum-to-drinking water ratio comes from studies involving populations exposed to PFOA through known contaminated drinking water sources in which there was a direct correlation between drinking water levels and serum levels. These studies concluded that consumption of water containing 1µg/L PFOA results in serum levels of approximately 100µg/L (Emmett et al., 2006 and Post et al., 2012). Once both measures are on a serum level metric, the background level from all exposure sources can be subtracted from the estimated serum level from drinking water exposure only to determine the percent of PFOA exposure from drinking water for the general population.

A PFOA-specific RSC factor was derived by first calculating a DWEL from the PFOA RfD of 0.006µg/kg/day (see section 5). For a standard adult weighing 70kg and drinking 2L/day the DWEL for PFOA is 0.21µg/L. The DWEL was converted to a PFOA serum level of 21µg/L through application of the 100:1 serum-to-drinking water ratio. The RSC was then calculated using the serum level associated with exposure through drinking water after accounting for background PFOA serum levels from NHANES biomonitoring studies (CDC NHANES, 2013).

The RSC is calculated as follows:

$$RSC = \frac{Serum\ level\ from\ drinking\ water\ exposure - Background\ Levels}{Serum\ level\ from\ drinking\ water\ exposure}\ x\ 100$$

$$PFOA\ RSC = \frac{21\mu g/L - 7.5\mu g/L}{21\mu g/L}\ x\ 100 = 64.3\%\ (rounded\ to\ 60\%)$$

5. PFOA Maximum Exposure Guideline Calculations

MECDC RfDs are calculated as follows:

$$RfD = \frac{POD}{uncertainty\ factors}$$

PFOA RfD calculation:

$$PFOA\ RfD = \frac{1.8\mu g/kg/day}{3\ x\ 10\ x\ 10} = 0.006\mu g/kg/day$$

where:
POD = the geometric mean of the human equivalent doses (0.0018mg/kg/day) converted to µg/kg/day
Uncertainty factors = 3-fold interspecies, 10-fold intraspecies and 10-fold database

MECDC MEGs for non-carcinogenic endpoints are calculated as follows:

$$MEG = \frac{RfD\ x\ BW}{WCR}\ x\ RSC$$

where:
BW = body weight in kilograms, 70kg standard adult
RSC = relative source contribution, default or data-driven RSC
WCR = water consumption rate in liters/day, 2L/day standard adult intake

PFOA MEG calculation:

$$PFOA\ MEG = \frac{0.006\mu g/kg/day\ x\ 70kg}{2L/day}\ x\ 0.6\ = 0.126\ \mu g/L$$

MECDC PFOA MEG = 0.1µg/L

6. Summary

Overall, the MECDC MEG for PFOA in drinking water of 0.1µg/L was developed using methods largely in line with USEPA guidelines for developing drinking water equivalent levels (USEPA, 2000). The MECDC PFOA MEG is within the range (0.04 – 1µg/L) of other health-based drinking water values for PFOA developed by the USEPA, New Jersey, Minnesota and North Carolina (Table 2). In comparison to PFOA serum levels and estimated drinking water levels that have been associated with adverse health effects from epidemiological studies involving PFOA, the MEG is within the range of some serum levels associated with adverse human health effects (Table 4). The MEG is slightly above serum levels associated with immune suppression in children. However, these immunological studies involved exposures to PFOA and PFOS, additional PFCs and possibly other immunosuppressive contaminants. Consequently, it is difficult to fully assess the sole impact of PFOA on immune responses in these studies due to the presence of other immunosuppressive contaminants. It will be important to stay up to date with emerging epidemiological studies to better assess the relevance of the MECDC PFOA MEG. The MEG was developed using the available risk assessments and primary peer-reviewed literature. The USEPA is in the process of developing a RfD for lifetime exposures and subsequent maximum contaminant level for PFOA in drinking water and have recently released a draft PFOA risk assessment for public comment and peer-review[7]. The MECDC may consider revision of the current PFOA MEG once the USEPA draft PFOA risk assessment and RfD have gone through public and peer-review and a final PFOA RfD published.

[7] https://peerreview.versar.com/epa/pfoa/

Table 4. PFOA serum levels associated with adverse human health effects and corresponding estimated PFOA drinking water levels using a 100:1 serum-to-drinking water concentration ratio.

	PFOA Serum Level Ranges (ng/mL)	Estimated PFOA Drinking Water Levels (µg/L)
General toxicity		
Pregnancy-induced hypertension C8 studies, Darrow et al., 2013	6.9 – 11.1 [a]	0.07 – 0.1
High cholesterol (≥240mg/dL) C8 studies, Steenland et al., 2009	13.2 – 26.5 [b]	0.1 – 0.3
Thyroid disease (any reported thyroid disease) NHANES 99 – 06, Melzer et al., 2010	5.7 – 123.0 [c]	0.06 – 1.2
Immune effects		
Reduced vaccine antibody levels in children Faroe Islands, Grandjean et al., 2012	3.33 – 4.96 [d]	0.03 – 0.05
Reduced vaccine antibody levels in children Norwegian mother child cohort, Granum et al., 2013	0.2 – 2.7 [e]	0.002 – 0.03
Reduced influenza vaccine antibody levels in adults C8 studies, Looker et al., 2013	13.8 – 2140 [f]	0.1 – 2.1

a. Serum range represents significant adjusted odds ratio for 2nd quintile as compared to referent 1st quintile (0-<6.9ng/mL) for pregnancy induced hypertension for all cohort births (Darrow et al., 2011, Table 4).
b. Serum range represents significant odds ratio for 2nd quartile as compared to referent 1st quartile (0-<13.2ng/mL) for hypercholesterolemia (Steenland et al., 2009, logistic regression results)
c. Serum range represents significant adjusted odds ratio 4th quartile as compared to referent 1st quartile (0.1-2.6ng/mL) for thyroid disease ever/thyroid disease current with medication for women (Melzer et al., 2010, Table 3 and Table 4).
d. Serum range represents the interquartile serum range at age 5 corresponding with a significant odds ratio for inadequate post-booster tetanus and diphtheria antibody levels in children at age 7 (Grandjean et al., 2012, Table 2 and eTable 4).
e. Serum range represents the maternal minimum and maximum serum levels corresponding with a significant decrease in rubella vaccine antibody levels and a significant increase in number of common colds from bivariate and multivariate linear regression analysis of children at age 3 (Granum et al., 2013, Table 3, Table 4 and Table 5).
f. Serum range represents significant findings for both the 2nd (13.8-31.5ng/mL) and 3rd (31.6-90ng/mL) quartiles for a decrease in influenza A/H3N2 antibody titer rise and the 4th quartile (90.1-2140ng/mL) for a decrease in influenza A/H3N2 antibody titer ratio as compared to the referent 1st quartile (0.25-13.7ng/mL) (Looker et al., 2013, Table 3).

7. References

Anderson, M.E. 2008. Perfluoroalkyl Acids and Related Chemistries-Toxicokinetics and Modes of Action. Tox Sci. 102(1): 3-14.

Barry, V., Winquist, A., and Steenland, K. 2013. Perfluorooctanoic Acid (PFOA) Exposures and Incident Cancers among Adults Living Near a Chemical Plant. Environ Health Perspect. 121(11-12): 1313-1318.

Bartell, S.M., Calafat, A.M., Lyu, C., Kato, K., Ryan, P.B., Steenland, K. 2010. Rate of Decline in Serum PFOA Concentrations after Granular Activated Carbon Filtration at Two Public Water Systems in Ohio and West Virginia. Environ Health Perspect. 118: 222-228.

Biegel, L.B., Hurtt, M.E., Frame, S.R., O'Connor, J.C., Cook, J.C. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol Sci. 60: 40-55.

Butenhoff, J., Costa, G., Elcombe, C., Farrar, D., Hansen, K., Iwai, H., Jung, R., Kennedy, G., Lieder, P., Olsen, G., Thomford, P. 2002. Toxicity of Ammonium Perfluorooctanoate in Male Cynomolgus monkeys after Oral Dosing for 6 Months. Toxicol Sci. 69: 244-257.

Butenhoff, J.L., Gaylor, D.W., Moore, J.A., Olsen, G.W, Rodricks, J., Mandel, J.H., Zobel, L.R. 2004. Characterization of risk for general population exposure to perfluorooctanoate. Regul Toxicol Pharmacol. 39: 363–380.

C8 Science Panel. 2012. C8 Probable Link Reports. http://www.c8sciencepanel.org/prob_link.html

CDC NHANES. 2013. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, September 2013. http://www.cdc.gov/exposurereport/

DeWitt, J.C., Shnyra, A., Badr, M.Z., Loveless, S.E., Hoban, D., Frame, S.R., Cunard, R., Anderson, S.E., Meade, B.J., Peden-Adams, M.M., Luebke, R.W., Luster M.I. 2009. Immunotoxicity of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and the Role of Peroxisome Proliferator-Activated Receptor Alpha. Crit Rev Toxicol. 39: 76-94.

Darrow, L.A., Stein, C.R., Steenland, K. 2013. Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005-2010. Environ Health Perspect. 121(10): 1207-13.

DeWitt, J.C., Peden-Adams, M.M., Keller J.M., Germolec, D.R. 2012. Immunotoxicity of Perfluorinated Compounds: Recent Developments. Toxicol Path. 40: 300-311.

EFSA. 2008. European Food Safety Authority. Opinion of the Scientific Panel on the Contaminants in the Food Chain on Perfluorooctane sulfonate (PFOS) and Perfluorooatanoic acid (PFOA) and their Salts. 2008. EFSA Journal 653: 1-131.

Emmett, E.A., Shofer, F.S., Zhang, H., Freeman, D., Desai, C., Shaw, L.M. 2006. Community exposure to perfluorooctanoate: Relationships between serum concentrations and exposure sources. JOEM. 48 (8): 759-770.

Eriksen, K.T., Sørensen, M., McLaughlin, J.K., Lipworth, L., Tjønneland, A., Overvad, K., et al. 2009. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J Natl Cancer Inst. 101: 605–609.

Gallo, V., Leonardi, G., Genser, B., Lopez-Espinosa, M.J., Frisbee, S.J,, Karlsson, L., Ducatman, A.M., Fletcher, T. 2012. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. Environ Health Perspect. 120(5): 655-60.

Geiger, S.D., Xiao, J., Shankar, A. 2012. Positive association between perfluoroalkyl chemicals and hyperuricemia in children. Am J Epidemiol. 177(11): 1255-62

Grandjean, P., Anderson, E.W., Budtz-Jorgensen, E., Nielsen, F., Molbak, K., Weihe, P. Heilmann, C. 2012. Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds. JAMA. 307 (4): 391-397.

Grandjean, P., Budtz-Jorgensen, E. 2013. Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children. Enviro Health. 12(1): 35.

Granum, B., Haug, L.S., Namork., E., Stolevik, S.B., Thomsen, C., Aaberge, I.A., Loveren, H.V., Lovik, M., Nygaard, U.C. 2013. Pre-natal exposure to perfluoroalkyl substances may be associated with alterd vaccine antibody levels and immune-related health outcomes in early childhood. J Immunotoxicol. 10(4): 373-379.

Halldorsson, T.I., Rytter, D., Haug, L.S., Bech, B.H., Danielsen, I., Becher, G., Henriksen, T.B., Olsen, S.F. 2012. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ Health Perspect. 120(5): 668-73.

Kato, K., Wong, L.Y., Jia, L.T., Kuklenyik, Z., Calafat, A.M. 2011. Trends in Exposure to Polyfluoroalkyl Chemicals in the U.S. Population: 1999−2008. Environ Sci Technol. 45 (19): 8037-8045.

Kristensen, S.L., Ramlau-Hansen, C.H., Ernst, E., Olsen, S.F., Bonde, J.P., Vested, A., Halldorsson, T.I,, Becher, G., Haug, L.S., Toft G. 2013. Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. Hum Reprod. 28(12): 3337-48.

Lau, C., Anitole, K., Hodes, C., Lai, D., Pfahles-Hutchens, A., Seed, J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol Sci. 99(2): 366-94.

Lau, C., Thibodeaux, J.R., Hanson, R.G., Narotsky, M.G., Rogers, J.M., Lindstrom, A.B., Strynar, M.J. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci. 90(2): 510-518.

Lopez-Espinosa, M.J., Mondal, D., Armstrong, B., Bloom, M.S., Fletcher, T. 2012. Thyroid function and perfluoroalkyl acids in children living near a chemical plant. Environ Health Perspect. 120(7): 1036-41.

Looker, C., Luster, M.I., Calafat, A.M.., Johnson, V.J., Burleson, G.R.., Burleson, F.G., Fletcher, T. 2013. Influenza vaccine response in adults exposed to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS). Toxicol. Sci. 138(1): 76-88.

Lorber, M., Egeghy, P.P. 2011. Simple Intake and Pharmacokinetic Modeling to Characterize Exposure of Americans to Perfluoroctanoic Acid, PFOA. Environ Sci Technol. 45: 8006–8014.

Macon, M.B., Villanueva, L.R., Tatum-Gibbs, K., Zehr, R.D., Strynar, R.D., Stanko, J.P., White, S.S., Helfant, L., Fenton, S.E. 2011. Prenatal Perfluorooctanoic Acid Exposure in CD-1 Mice: Low-Dose Developmental Effects and Internal Dosimetry. Tox Sci. 122(1): 134-145.

Maine Center for Disease Control and Prevention. 2011. Maximum Exposure Guidelines for Drinking water. Department of Health and Human Services, Maine Center for Disease Control and Prevention, Environmental and Occupational Health Program. http://www.maine.gov/dhhs/mecdc/environmental-health/eohp/wells/

Melzer, D., Rice, N., Depledge, M.H., Henley, W.E., Galloway, T.S. 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. Environ Health Perspect. 118(5): 686-92.

Minnesota Department of Health. 2008. Health Risk Limits for Perfluorochemicals – Finial Report to the Minnesota Legislature 2008. http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/reports.html

NCSAB. 2012. Recommendation to the Division of Water Quality for an Interm Maximum Allowable Concentration for Perfluorooctanoic Acid (PFOA) in Groundwater. Division of Air quality, The Secretary's Science Advisory Board on Toxic Air Pollutants. http://daq.state.nc.us/toxics/risk/sab/ra/

Nelson, J.W., Hatch, E.E., Webster, T.F. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environ Health Perspect. 118(2): 197-202.

New Jersey Department of Environmental Protection. 2007. Guidance for PFOA in Drinking Water at Pennsgrove Water Supply Company. State of New Jersey Department of Environmental Protection, Division of Science, Research and Technology. Memorandum. http://www.nj.gov/dep/watersupply/dwc_quality_pfoa.html

Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L.R. 2007. Half-Life of Serum Elimination of Perfluorooctanesulfonate, Perfluorohexanesulfonate, and Perfluorooctanoate in Retired Fluorochemical Production Workers. Environ Health Perspect. 115: 1298-1305.

Perkins, R.G., Butenhoff, J.L., Kennedy, G.L., and Palazzolo, M.J. 2004. 13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drun Chem Toxicol. 4: 361-378.

Post, G., Cohn, P.D., Cooper, K.R. 2012. Perfluorooctanoic Acid (PFOA), an emerging drinking water contaminant: A critical review of recent literature. Environ Res. 116: 93-117.

Sibinski, L.J., Allen, J.L., Erickson, E.E. 1983. Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats. Experiment No. 0281CR0012, Riker Laboratories Inc., St. Paul MN. USEPA Public Docket AR-226-0437, 0438, 0439 and 0440. (Available as Butenhoff, J.L., Kennedy, G.L., Chang, S.C., Olsen, G.W. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology. 298 (1-3): 1-13.)

Steenland, K., Fletcher, T., Savitz, D.A. 2010. Epidemiologic evidence on the health effects perfluorooctanoic acid (PFOA). Environ Health Perspect. 118: 1100-1108.

Steenland, K., Tinker, S., Frisbee, S., Ducatman, A., Vaccarino, V. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. Am J Epidemiol. 170(10): 1268-78.

Steenland, K., Zhao, L., Winquist, A., Parks, C. 2013. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. Environ Health Perspect. 121(8): 900-5.

USEPA. 1990. Risk Assessment, Management and Communication of Drinking Water Contamination. EPA/625/4-89/024.

USEPA. 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. EPA-822-B-00-004.

USEPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F.

USEPA. 2005. Draft Risk Assessment of the Potential Human Effects Associated with Exposure to Perfluorooctanoic Acid and Its Salts. Office of Pollution Prevention and Toxics Risk Assessment Division.

USEPA. 2006. SAB Review of EPA's Draft Risk Assessment of Potential Human Health Effects Associated with PFOA and Its Salts. EPA-SAB-06-006.

USEPA. 2009. Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). Office of Water. October 28, 2009.

USEPA. 2011. Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose. EPA/100/R11/0001.

USEPA. 2012. Benchmark Dose Technical Guidance. EPA/100/R-12/001.

Vested, A., Ramlau-Hansen, C.H., Olsen, S.F., Bonde, J.P., Kristensen, S.L., Halldorsson, T.I., Becher, G., Haug, L.S., Ernst, E.H., Toft, G. 2013. Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men. Environ Health Perspect. 121(4): 453-8.

Vieira, M.N., Hoffman, K., Shin, H., Weinberg, J.M., Webster, T.F., Fletcher, T. 2013. Perfluorooctanoic Acid Exposure and Cancer Outcomes in a Contaminated Community: A Geographic Analysis. Environ Health Perspect. 121(3): 318-323.

White, S.S., Fenton, S.E., Hines, E.P. 2011a. Endocrine disrupting properties of perfluorooctanoic acid. J Steroid Biochem Mol Biol. 127(1-2): 16-26.

White, S.S., Stanko, J.P., Kato, K., Calafat, A.M., Hines, E.P., Fenton, S.E. 2011b. Gestational and Chronic Low-Dose PFOA Exposure and Mammary Gland Growth and Differentiation in Three Generations of CD-1 Mice. Environ Health Perspect. 119: 1070-1076.

Winquist, A., Lally C., Shin, H.M., Steenland, K. 2013. Design, methods, and population for a study of PFOA health effects among highly exposed mid-Ohio valley community residents and workers. Environ Health Perspect. 121(8): 893-899.

Winquist, A., Steenland, K. 2014. Perfluorooctanoic Acid exposure and thyroid disease in community and worker cohorts. Epidemiology. 25(2): 255-64.

Yang, C., Tan, Y.S, Harkema, J.R., Haslam, S.Z. 2009. Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. Reprod Toxicol. 27(3-4): 299-306.